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13. ABSTRACT (Maximum 200 Words)

The goal of this project is to test the hypotheses that: 1.) *Subjects with GWI have reduced NAA in the basal ganglia and pons, which are not accounted for by confounds such as depression, post traumatic stress disorder, and alcoholism.* 2.) *Reduced NAA in basal ganglia and pons correlates with CNS signs and symptoms of GWI.*

Thus far we have mailed out a total of 505 letters describing our study. Dr Weiner appeared on several radio and TV programs, in response to our press release. Over 262 subjects have contacted us expressing interest in this study. Since we began enrolling subjects, we have largely met our goals of studying 2 subjects/week with the complete study battery which includes medical evaluation, neuropsychological testing, startle testing, MRI/MRS and the "Haley Questionnaire." Thus far, we have studied a total of 84 subjects. At this time, 22 of these subjects have met the criteria for GWI and 26 are controls, with 36 having an intermediate classification. We currently have 5 subjects scheduled for study for the remainder of the month. Although some preliminary data analysis has been performed, at the current time the sample size is much too small for any formal data analysis.

14. SUBJECT TERMS
Gulf War Illness, Gulf War Syndrome, Magnetic Resonance Imaging, Magnetic Resonance Spectroscopy, Human Brain, Neuro-psychological testing, audio vestibular testing, PTSD

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INTRODUCTION: The primary goal of this project is to test the a priori hypotheses that: 1.) Subjects with Gulf War Illness (GWI) have reduced N-acetyl aspartate (NAA) in the basal ganglia and pons, which are not accounted for by confounds such as alcohol abuse, post traumatic stress disorder (PTSD) and depression. 2.) Reduced NAA in basal ganglia and pons correlates with central nervous system (CNS) signs and symptoms of GWI. This project proposes to replicate and extend previous findings of Haley et al. on 200 subjects with Gulf War Illness (GWI) and 200 Gulf War Veteran (GWV) controls drawn from Northern California and surrounding regions. To date we have enrolled 84 subjects into the study.

BODY: Thus far 55 subjects have been recruited, studied, and have data for analysis. Subjects were categorized as GW veterans (i.e. healthy controls), GW Illness (who meet CDC criteria), or intermediate. The following table summarizes various demographic variables. "CAPS current" represents the mean score of the frequency and severity of the CAPS (a measure of PTSD) on a scale from 0-4 on a total of 17 symptoms of post-traumatic stress. "Current drinking" represents the mean number of alcoholic drinks consumed monthly. "GWI severity" represents the mean score of Gulf War Illness determined by the medical practitioner's clinical judgment.

Summary Variables

	GW Veteran	Intermediate	GW Illness
N	16	23	16
Age	43.36 ± 9.59	45.76 ± 12.58	42.25 ± 9.68
Education	15.13 ± 2.66	14.00 ± 1.98	14.19 ± 1.80
CAPS Current	10.00 ± 16.86	17.30 ± 22.17	32.50 ± 24.49
Current Drinking	7.25 ± 9.36	24.45 ± 43.63	10.50 ± 18.26
GWI Severity	1.67 ± 0.58	1.73 ± 0.79	3.25 ± 1.00

The following tables (Table 1 and 2) summarize preliminary spectral data. NAA is a measure of neuronal density or integrity and can be measured as absolute NAA or a ratio to other metabolites.

Table 1 suggests that GW Illness may be associated with reduced NAA in the Right Basal Ganglia, consistent with previous results from Haley et al.

Table 1: GW Spectral Data
Mean Absolute NAA

	GW Veteran	Intermediate	GW Illness
Left BG	66.50 ± 9.26 n=14	65.03 ± 7.36 n=16	67.71 ± 6.45 n=15
Right BG	62.32 ± 4.77* n=12	60.37 ± 6.31 =15	58.90 ± 5.69* n=13
Pons	26.39 ± 3.64 n=9	29.12 ± 9.71 n=15	26.31 ± 4.49 n=11

*p-value = 0.06, GW Veteran > GW Illness

In contrast with the results of Haley et al., Table 2 suggests that GW Illness has higher NAA in left basal ganglia (BG) than controls.

Table 2: GW Spectral Data
Mean NAA/ (Cr + Cho)

	GW Veteran	Intermediate	GW Illness
Left BG	1.21 ± 0.12 n=14	1.17 ± 0.07* n=16	1.25 ± 0.07* n=15
Right BG	1.20 ± 0.12 n=12	1.20 ± 0.14 n=15	1.17 ± 0.10 n=13
Pons	1.24 ± 0.20 n=9	1.26 ± 0.22 n=15	1.17 ± 0.27 n=11

*p-value = 0.003, Intermediate < GW Illness

Haley Factor Analysis

We have obtained data from our subjects using the identical questionnaire designed by Haley et al. Furthermore, we have analyzed the data using software provided by Haley, but our staff are collecting and analyzing all data. The preliminary results of the Haley Factor Analysis has shown the following trends:

1. The distribution of factor scores by diagnostic category shows that a Gulf War Syndrome (GWS) also known as Gulf War Illness (GWI) diagnosis is correlated with a higher score which is clearest in factor 3 (central pain). There are relatively few people in the intermediate score range and the onset year is highly concentrated towards 1991.

2. There is a relationship between diagnosis and factor score category. Those with high factor scores are usually diagnosed as ill. Those diagnosed as ill have a wide range of factor scores.

3. There is a relationship between factor scores and year of onset. Those diagnosed as ill have higher factor scores and factor scores are clearly higher in earlier onset years than later ones.

4. There is a pattern of high factor scores and their frequency. Usually only one factor is exhibited. When more than one factor is exhibited, it is usually 2 and 3. All three factors are never exhibited. There is a correlation between factors exhibited and all 4 alternative indicators.

5. The following trends were noted with Factor 1 Questions:
High factor 1 scorers tend not to have problems with sense of direction.
High factor 1 scorers tend not to have problems with getting lost.
High factor 1 scorers tend to have problems with slurring.

6. The following trends were noted with Factor 2 Questions:
High factor 2 scorers tend to have problems being confused with what they are doing.
High factor 2 scorers tend to have problems being confused with where they are.
High factor 2 scorers tend to have problems getting lost.

High factor 2 scorers tend to have problems with sense of direction.
High factor 2 scorers tend to have problems making change.
High factor 2 scorers tend to have to hold a wall to stay up.
High factor 2 scorers tend to have problems where they feel they are spinning.
High factor 2 scorers tend not to be as depressed.
High factor 2 scorers tend not to be schizophrenic.

7. The following trends were noted with Factor 3 Questions:
High factor 3 scorers tend to have aching ankles, forearms, hips, upper arms, and wrists.
High factor 3 scorers tend to have weakness in their arms and legs.

Preliminary results of the SF-36V

The following table shows group differences between GW veteran, intermediate and GW illness subjects. Form 1 classification is based on only one CDC classification form administered. Strict classification is based on three similar forms administered at three times. The subjects who meet criteria for Gulf War Illness certainly show many significant differences with controls, indicating that they have multiple complaints and impaired functioning.

	Form 1 Classification			Strict Classification					
	GW Veteran	GW Illness	p-value	GW Veteran	Intermediate	GW Illness	p-value (Int vs. Vet)	p-value (Vet vs. Ill)	p-value (Int vs. Ill)
Physical Functioning	73.4	59.5	0.041	79.5	67.5	59.8	0.339	0.122	0.603
Role-Physical	71.3	48.0	<.0001	82.5	62.7	44.3	0.007	<.0001	0.007
Pain Index	60.4	47.3	0.027	70.4	54.3	45.0	0.064	0.008	0.341
General Health Perceptions	44.4	60.2	0.004	35.0	50.7	63.0	0.047	0.001	0.112
Vitality	61.8	55.3	0.039	64.0	60.6	52.5	0.644	0.033	0.075
Social Functioning	81.3	50.7	<.0001	91.3	71.3	46.9	0.052	<.0001	0.008
Role-Emotional	83.1	57.0	<.0001	92.5	73.5	55.6	0.050	0.001	0.050
Mental Health Index	42.4	62.7	<.0001	35.6	48.1	67.3	0.012	<.0001	<.0001
Overall			0.000						0.001
Physical Component Scale	44.1	38.2	0.005	47.2	41.9	37.3	0.089	0.003	0.121
Mental Component Scale	43.9	42.3	0.326	44.1	43.1	43.0	0.894	0.904	0.999
Overall			0.005						0.017

Paraoxonase Analysis

Paraoxonase 1 (PON1) status was determined for 74 individuals (x controls and y subjects). As expected, a plot of rates of diazoxon hydrolysis vs. paraoxon hydrolysis divided the population into three distinct groups, individuals functionally homozygous for PON1-Q192 or PON1-R192 and heterozygotes. The functional enzyme analysis provides both an accurate inference of the amino acid present at position 192, which determines catalytic efficiency for hydrolysis of some substrates and at the same time provides the level of plasma PON1 for the individual. Both of these parameters are important in determining an individual's sensitivity or resistance to a given exposure. We are in the process of plotting the rates of hydrolysis for each group (GW veteran, intermediate, and GW illness).

KEY RESEARCH ACCOMPLISHMENTS:

- Staff hired and trained.
- Study manuals and protocols developed.
- UCSF, VA, and DOD IRB approvals obtained.
- Subject recruitment letters sent out: 505
- Subjects called for informational packet: 262
- Subjects entered into the study: 84
- Subject recruitment is on schedule as described in the grant application.
- Began analyzing preliminary data.

REPORTABLE OUTCOMES:

- No publications at this early stage of the project.
- NIH MR and Spectroscopy of Human Brain in Gulf War Illness Conference. Talk was entitled: Magnetic Resonance and Spectroscopy of Human Brain in Gulf War Illness. February 19th, 2002.
- VA Head Quarters in Washington DC Meeting on Magnetic Resonance and Spectroscopy of Human Brain in Gulf War Illness. May 26th, 2003.
- Awarded $500k supplement toward the purchase of a 4 Tesla magnet.

CONCLUSIONS: After one and a half years of this project, the major conclusion is that our previous uncontrolled results appeared to be consistent with reduced NAA in the right basal ganglia. Some of our recent results also are consistent with reduced NAA in the right basal ganglia, but the increased NAA ratios in the left basal ganglia of Gulf War Illness contradicts the previous reports of Haley. However, thus far none of our data has been corrected for confounds of PTSD, depression or alcoholism.